P334

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The Microbe's Contribution to Biology–50 years after

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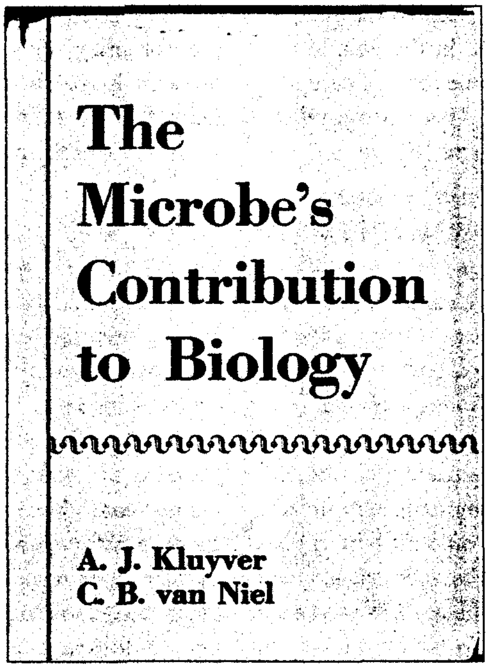
Just 50 years ago, A. J. Kluyver and C. B. van Niel ventured a concise oversight: they published *The Microbe's Contribution to Biology*. One might ponder deeply what is meant by a "contribution" to biology, and at equal length deconstruct the boundaries of "microbe". Famously, you know one when you see it—but here the object is invisible, and it is mainly by its fruits that you detect a microbe. The year 1906 corresponded to the beginning of robust expectations about the stable continuity of shape, form, and metabolic capacity, even of these invisible particles. But one could hardly find mention of bacteria in the same breath as garden peas, except perhaps to report a new and troublesome pest. Nor could there be in the face of a rigorous dogma denying any mode of reproduction beyond binary fission for bacteria.



Up through the first half of the 20th century, the microbes' main contribution was the assertion of the broadest imaginable exploitation of biochemical niches, and at the same time the matching of those metabolic skills with those of the macrobial world. These were sufficiently numerous—look, for example, at the continuity of cellular cytochromes, or of the Krebs cycles in nitrogen metabolis—to support the doctrine of the biochemical unity of all life: an engineering design that encompassed recycling via putrefaction by microbes of shared infrastructures. Even huge whales and redwoods are merely hiccups in the flow of solar energy.

Microbes exhibit a special advantage both in the laboratory and in the extended world: their tiny size and huge population dimensions enable easy searches, with Nature providing most of the labor. Soils, the deep seas, our own bodies—warm or begone—or similar habitats will allow for selective outgrowth of a peculiar biotype. The experiments of nature are innumerable, and we but sample them with our probes. It would be a mistake to assume that we have already even nearly exhausted the biodiversity awaiting that sampling: a correlative lead that animates our own research projects would point to still-to-be-catalogued libraries of growth factors that are part of the strange structures and functions belying further occupation of new territories.

By 1956, there were strenuous debates about the place that bacteria could occupy in any (scala naturae) comprehensive scheme. Rene Dubos (*The Bacterial Cell*, 1945) was nearly unique in his serious reference to "cells". Most writers were impressed by the bacteria's apparent deficit in mitotic spindles, then cytokinesis, or indeed, of many of the organelles that routinely populate larger cells and organs. The Bacteria were routinely swept under the rug in biology textbooks, which in turn were subdivided into those covering botany or zoology. Dubos figured Robinow's "nuclei" but, in what were later to be designated as prokaryotes, they were only half there: in modern terms: DNA aggregates "yes", but nuclear membrane "no".

Microbiology was preeminently a medical discipline, associated with the study of dire disease. Nevertheless, one further function stood out in the terrestrial economy. We were reminded from time to time of the necessity of bacteria as frontline garbage recyclers, and the luxuries offered by frontline fermenters for the production of bread, cheese, and wine. Such fermentations were associated with "adaptive enzyme formation", e.g., of lactase. Convenient laboratory systems facilitated study of the efficient avoidance of gratuitous enzyme synthesis, such that bacterial inventories of catabolases are maintained only in the presence of the specific substrate. Similar regulatory complexes can be found in eukaryotes, but only rarely; whereas some pseudomonads may well display adaptive enzymes for scores if not hundreds of substrates. Substrate-induced enzymes have had diverse interpretations, including target induced shapes. In the end, almost every example has been enfolded into some form of derepression of a gene-controlled respondent. This operon-related model has since been expanded to account for the antibody response of prefigured immunocytes. In a word, the host cells provide the shape diversity, out of which the best fits are selected. However, the attractive imagery, promulgated by Haurowitz and Pauling, of substrate-induced (vs. -selected) fits has simply not worked out in biological systems. Instead, the selectionist model now appears to permeate what has evolved on earth's biota. Molecular imprinting during polymer renaturation has made an appearance in the physical nonbiological literature.

The greatest glory for *Microbe's* has issued from studies of the pneumococcus. It fell upon Avery, Macleod, and McCarty (1944) to clarify Griffith's (1928) study of pneumococcus transformation. To boot, the trio's purification of the type-active extracts elicited the surprise of the century, namely that their activity rested in DNA, thus sparking the genomic revolution of the 20th century. Put simply, the transformation provided a direct assay for biological capacity, e.g., to support the synthesis of a specific activity. As often as not, this was encapsulated in a bacterial cell or virus. We then needed to learn the bugs' own tricks for conveying or blocking infectious transmission. A footnote to acknowledge the centrality of bacteriophage research: the hosts are infected cell by cell in a fashion common to microbial and macrobial hosts.

The microbial skills relevant to this outcome have been: (i) the ease of recognizing rare genomic alterations, and (ii) the unexpected proclivity for the uptake of DNA, raw or in phage, so that it could be embodied in a gene assay.

We are reminded once again of the August Krogh principle: for any given scientific challenge there is a critter fittest towards its solution. Conversely, the domestication of any animal, plant, or microbe opens new opportunities and pathways shaping the evolution of a discipline.